Editorial

What Is the Role of Testing for IgM Antibody to Core Antigen of Hepatitis B Virus?

The clinician confronted with a hepatitis B virus surface antigen (HBsAg)-positive patient with elevated serum aminotransferase activities must consider several possibilities. First, the patient could be experiencing an acute infection with hepatitis B virus (HBV), as approximately 85 to 90% of such patients still have antigenemia at the time they seek medical attention. Alternatively, the possibility exists that the patient may be chronically infected with HBV and that current symptoms and laboratory findings reflect an ongoing chronic hepatitis. The clinician must also consider whether hepatitis delta virus could be playing a role, either as an acute coinfection with HBV or as a superinfection complicating a long-standing and perhaps previously asymptomatic HBV carrier state. Finally, the patient's liver function abnormalities could be a manifestation of non-A, non-B hepatitis, unrelated to an underlying chronic HBV infection. Risk factors for acquiring non-A, non-B hepatitis overlap substantially with risk factors for hepatitis B; thus, the probability of such an event is increased. When a physician is confronted with these clinical possibilities, the presence or absence of IgM antibody to the core antigen of HBV (IgM anti-HBc) provides a useful indication of the nature of the HBV infection. Simply stated, almost all patients with acute hepatitis B have high titers of IgM anti-HBc at the time of initial examination, whereas chronic carriers of the virus have only low titers or no detectable IgM anti-HBc at all. The presence of high-titer IgM anti-HBc generally indicates the patient has acute hepatitis B (hepatitis delta coinfection is not excluded), whereas a negative test in a HBsAg-positive patient with hepatitis should prompt the consideration of other possibilities, especially hepatitis delta superinfection or intercurrent non-A, non-B hepatitis.

With respect to the diagnosis of acute hepatitis B, IgM anti-HBc is arguably the best serologic marker. Approximately 5 to 10% of cases manifest after clearance of HBsAg from the blood and before the appearance of antibody to the surface antigen (the so-called window period), whereas a similar proportion of patients may already test positive for antibody to the surface antigen by the time they seek medical attention. Thus, the sensitivity of IgM anti-HBc is superior to that of HBsAg as a marker of acute hepatitis B because a substantial proportion of patients lack detectable HBsAg. In contrast, IgM anti-HBc is detected in almost all acutely infected persons. The specificity and hence utility of IgM anti-HBc as a test procedure, however, are potentially threatened by the persistence of IgM anti-HBc in some patients with chronic hepatitis B. The article by Czaja and associates in this issue of the Proceedings (pages 119 to 125) adds to and extends previous observations of IgM anti-HBc in such patients.

Czaja and co-workers show that a substantial proportion of HBsAg-positive patients under surveillance at a major medical center because of clinical, biochemical, or histologic evidence of severe chronic active hepatitis have persistent, albeit fluctuating IgM anti-HBc levels. This antibody was found in 12 of 16 such patients by using a commercially available, enzyme-linked immunoassay (Corzyme-M, Abbott Laboratories, North Chicago, Illinois). These data are somewhat surprising because this particular assay is applied to serum only after it has been diluted a thousandfold. This dilution step is included in the assay in order to improve its specificity for acute infection and has resulted in negative test results in most chronic carriers tested by investigators at my institution and elsewhere. These and other data, however, make it clear that the positive predictive value of IgM anti-HBc varies with the frequency of HBsAg carriers in the population to be tested and the proportion of these carriers who may have detectable IgM anti-HBc. The fluctuating positivity reported by Czaja and associates in these patients presumably reflects the presence of only low levels of IgM anti-
HBc, levels that are probably near the threshold for the assay. These results are consistent with previous results obtained by my colleagues and me with an antibody-capture radioimmunoassay for IgM anti-HBc. We found the geometric mean titer of IgM anti-HBc to be 1:191,000 or more in patients tested within 30 days after the onset of acute hepatitis B, in comparison with only 1:459 in a small group of persistently infected HBV carriers.

Confirming the results of previous investigators, Czaja and colleagues also report that the IgM anti-HBc is more likely to be found in chronic HBsAg carriers with active liver disease than in those with inactive disease and that HBsAg carriers with IgM anti-HBc are likely to have hepatitis B e antigen positivity or detectable viremia (HBV DNA positive by DNA-DNA hybridization). These data are consistent with earlier findings that suggested that the presence of IgM anti-HBc also correlated with the presence of detectable serum HBV DNA polymerase activity and with high levels of circulating HBsAg (more than 80 /ug/ml) (Table 1). In reviewing the data presented by Czaja and co-workers, however, readers must remember that the group of patients they studied was highly selected and not representative of HBV carriers in general. For example, although we found low titers of IgM anti-HBc in 29 of 33 chronic HBsAg carriers under surveillance in a liver disease clinic, IgM anti-HBc was present in only 12 of 20 healthy blood donors who were incidentally found to be HBsAg positive (P = 0.02). In this study, serum samples were tested by radioimmunoassay at a 1:100 dilution; thus, the test was probably more sensitive than that used by Czaja and associates.

The continued presence of IgM anti-HBc in many persistent carriers of hepatitis B virus and the apparent association of this antibody with active liver disease are curious factors that remain incompletely explained. Continuing IgM anti-HBc reactivity may relate to continued expression of the hepatitis B core antigen (HBcAg) and thus to higher levels of HBV replication, as suggested by Czaja and colleagues and others previously. Patients who are DNA polymerase, hepatitis B e antigen or HBV DNA positive are more likely than others to have detectable intrahepatic HBcAg, a fact that is not surprising when one considers that HBcAg is an integral component of the HBV virion. The potential link between IgM anti-HBc positivity and HBcAg expression is of special interest, however, because of evidence suggesting that HBcAg may be a target antigen for HLA-restricted cytotoxic T-lymphocytes putatively involved in the pathogenesis of chronic hepatitis associated with HBV persistence. Continuing IgM anti-HBc positivity may be a marker of HBcAg expression in infected hepatocytes, and this in turn may be associated with a high level of immune destruction of these cells. The relationship, however, may not be so simple. The destruction of infected hepatocytes by cytotoxic lymphocytes may also result in release of intracellular HBcAg, making sequestered antigen available for continued immune stimulation and thereby maintaining a continued low-level IgM antibody response. IgM anti-HBc positivity could reflect the level of intrahepatic HBcAg expression or could be a measure of destruction of HBcAg-containing cells. Both hypotheses might be correct.

Another curiosity concerning the persistence of IgM anti-HBc in chronic HBsAg carriers is that,
in most cases, the persisting antibody is of a low-
molecular-weight species. Most IgM antibodies associated with primary humoral immune responses (including IgM anti-HBc in acute HBV infections) are pentamer molecules with a sedimentation constant of 19S. In contrast, the IgM anti-HBc present in many chronic carriers is monomeric, with a sedimentation constant of 7S, similar to that of IgG. This observation suggests that assays specific for 19S antibody might have improved specificity for acute disease, although 19S antibody also persists in several chronic infections. In reviewing a series of IgM anti-HBc-positive patients with chronic hepatitis B, my colleagues and I detected no significant correlation with 19S or 7S antibody predominance other than the somewhat surprising finding that 19S antibody predominance was more commonly present in homosexual men who were HBsAg positive than in carriers from other risk groups. Distinguishing 19S from 7S antibody responses remains a tedious research laboratory procedure, with no apparent clinical relevance.

Where, then, does testing for IgM anti-HBc “fit” among the current armamentarium of HBV-specific serologic procedures? It remains, first and foremost, the best indicator of acute hepatitis B, considerably more sensitive and somewhat more specific than HBsAg testing alone. A more quantitative approach to anti-HBc determination could improve its specificity in this setting, however, as titers present in acute disease are considerably higher than those found in chronic carriers, with little overlap. Nonetheless, the aforementioned studies suggest an economic approach to the laboratory diagnosis of HBV infection in patients who have acute hepatitis. First, a screening procedure with use of a non-immunoglobulin class-specific assay such as a competitive-inhibition immunoenzymoassay should be performed to identify anti-HBc. All patients with acute or chronic HBV infections and many who have recovered from hepatitis B in the past will have a positive result of this assay. Second, in patients who test positive for anti-HBc, IgM anti-HBc and HBsAg tests should be conducted with the same serum specimen to assess whether the anti-HBc response is acute or long-standing and to determine whether the HBV infection remains active. The pattern of positivity in these assays may thus indicate the presence of acute hepatitis B (IgM anti-HBc positive, HBsAg negative), or the possibility of hepatitis delta super-infection (IgM anti-HBc negative but HBsAg positive), or a probable lack of involvement of HBV in current symptoms (both tests negative). The clinical utility of IgM anti-HBc is far less in the diagnosis of liver disease associated with chronic HBV infections. The presence of low titers of this antibody in many patients with active liver disease and persistent hepatitis B infection remains an interesting curiosity but has no diagnostic utility.

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